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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,314	07/02/2001	Olga Bandman	PF-0568 USN	5060

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EXAMINER	
CARLSON, KAREN C	
ART UNIT	PAPER NUMBER
1653	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,314	BANDMAN ET AL.	
	Examiner	Art Unit	
	Karen Cochrane Carlson, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election with traverse of Group 13, polynucleotides encoding SEQ ID NO: 6 (ie, SEQ ID NO: 14) in the paper filed March 29, 2004 is acknowledged. The traversal is on the ground(s) that unity must be applied in national stage applications, that Example 17 of Annex B states that polypeptides and polynucleotides share unity, that dependent claims should not be separated from independent claims, that a special technical feature unifies all claims, that the instant read over the prior art, and that at least the methods of using the polynucleotides of Group 13 should be examined with Group 13, that Markush claims should be examined in full, and that at least 10 nucleic acid sequences can be examined in a single application. This is not found persuasive because unity of invention was applied in the restriction requirement, and the sequences were divided up in the PCT – see its PCT 210. Further, art was found against the first invention in that Ryseck et al. anticipates Group 1 drawn to the polypeptide comprising SEQ ID NO: 1 and thus unity fails because there is no special technical feature even in Group 1 and therefore all products are distinct. A method is distinguishable from a product, regardless of whether the method depends from a product claim only to identify the product used or produced. Rejoinder practice will be applied if the nucleic acid sequence elected is allowable. Markush claims must comprise sequences having the similar structure and function, such that a single sequence can be searched as a representative of all sequences in the claims. In the instant application, the sequences differ in structure and in function and therefore do not form a proper Markush group when presented in a single claim. Further, up to 10 does not mean 10; rather, the sequences must be closely aligned to warrant the examination of 10 nucleic acid sequences.

The requirement is still deemed proper and is therefore made FINAL.

Upon review of the specification and the art, all claims as they pertain to SEQ ID NO: 6 and 14 were examined.

Priority is to July 31, 1998.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In Claims 21 and 23, the term "identical" is used. The term "identical" is an absolute term, that is, either something is identical to another thing or it is not. Applicants may wish to refer to the art-recognized term --- identity ----.

In Claims 21 and 23, the phrase "biologically active fragment" is used. It is not clear what the biological activity is such that one would know what activity a fragment should have.

The claims encompass non-elected sequences. Therefore, the claims are indefinite for not particularly pointing out and distinctly claiming the subject matter which the applicant regards as his elected invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 23, 26-28, 30-35, 37, 38, 39, and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification fails to provide written

description of polypeptides less than 100% identity to SEQ ID NO: 6, biologically active fragments of SEQ ID NO: 6, immunologically active fragments of SEQ ID NO: 6, polynucleotides encoding same or having less than 100% identity to SEQ ID NO: 14, wherein the polypeptide is MEA6, or the polynucleotide encodes MEA6.

In Table 2, at page 53 of the specification, indicates that SEQ ID NO: 6 (HCYT-6) has been identified as tropomyosin, receptors, and meningioma expressed antigen 6 (MEA6). At page 14, para. 3 of the specification, the specification states that HCYT-6 has chemical and structural similarity with tropomyosin isoforms. The specification states that the N -terminus of HCYT-6 (SEQ ID NO: 6) has homology to tektins, and the intervening regions of HCYT-6 has homology to tropomyosin isoforms. The C-terminus of HCYT-6 has homology to receptors. Throughout the specification, SEQ ID NO: 6 is stated to be a human cytoskeletal protein such as tropomyosin and all discussion is focused on SEQ ID NO: 6 being a cytoskeletal protein. At page 24, para. 1, for example, it is stated that chemical and structural similarity, e.g., in the context of sequences and motifs, exists between HCYT and human cytoskeletal proteins. In addition, HCYT is expressed in tissues associated with cancer, cell proliferation, fetal development and inflammation and the immune response, as well as in reproductive, nervous, cardiovascular, developmental, and gastrointestinal tissues. Therefore, HCYT appears to be involved with cell proliferation, immunological, vesicle traficking, reproductive, smooth muscle, developmental, and nervous disorders. Indeed, the disorders that HCYT can be use to treat at pages 24-26 do not mention meningioma.

Heckel et al. (1997; Human Molecular Genetics 6(12): 2031-2041) teach MEA6 which shares 92.7% identity with SEQ ID NO: 6. A sequence search did not provide any art drawn to tropmyosin or other cytoskeletal proteins. Thus, SEQ ID NO: 6 is not a intracellular cytoskeletal protein like tropomyosin, but rather an extracellular antigen expressed from meningiomas. Thus, the specification fails to provide written description of polypeptides less than 100% identity to

SEQ ID NO: 6, biologically active fragments of SEQ ID NO: 6, immunologically active fragments of SEQ ID NO: 6, polynucleotides encoding same or having less than 100% identity to SEQ ID NO: 14, wherein the polypeptide is MEA6, or the polynucleotide encodes MEA6, or antibodies specific to SEQ ID NO: 6 (including fragments thereof).

The specification fails to describe a method for screening compounds that bind even to MEA6 (Claim 37) because this method is drawn to SEQ ID NO: 6 being like tropomyosin. At page 31, para. 1:

> In another embodiment of the invention, HCYT, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between HCYT and the agent being tested may be measured.

The specification does not teach a method for screening compounds that modulate the activity of SEQ ID NO: 6 (Claim 38), whether it is a cytoskeletal protein or MEA6. Note that MEA6 has no known function but to be an antigen; thus one cannot know how to modulate its activity. Applicants refer to page 31, para, 1 and Example XIV at page 49, but no such method is disclosed. At page 31, pharmaceutical compositions are disclosed.

Example XIV refers to a binding assay for cytoskeletal proteins and reads:

> HCYT, or biologically active fragments thereof, are labeled with ^{125}I Bolton-Hunter reagent. Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled HCYT, washed, and any wells with labeled HCYT complex are assayed. Data obtained using different concentrations of HCYT are used to calculate 35 values for the number, amount, and association of HCYT with the candidate molecules.

Thus, a method for screening compounds that modulate the activity of SEQ ID NO: 6 is new matter.

The specification does not teach a method for screening compounds that change the expression of SEQ ID NO: 14 (Claim 39) or a method for assessing toxicity of a test compound via

nucleic acid expression profiling (Claim 41). Applicants refer to page 33, lines 2-8, page 33, line 34 to page 34 line 5, page 38, lines 2-7, and page 37, lines 6-18 as basis for these claims.

Page 33, lines 2-8 refers to determine therapeutic indexes for protein and states:

> Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED50 (the dose therapeutically effective in 50% of the population) or LD50 (the dose lethal to 50% of the population) statistics. The dose ratio of therapeutic to toxic effects is the therapeutic index, and it can be expressed as the ED50/LD50 ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use.

Page 33, line 4 to page 34, line 5 refers to the identification of protein and states:

> A variety of protocols for measuring HCYT, including ELISAS, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of HCYT expression. Normal or standard values for HCYT expression are established by combining body fluids or cell extract taken from normal mammalian subjects, preferably human, with antibody to HCYT under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of HCYT expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

Page 38, lines 2-7 refers to microarrays and hints at monitoring therapeutic agent and states:

> In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

Page 38, lines 6-18 refers to changes in nucleic acid expression of HCYT for diagnosis of a disorder and then a treatment protocol, but no compounds that effect expression of HCYT but rather treat symptoms of the disorder are provided:

> In order to provide a basis for the diagnosis of a disorder associated with expression of HCYT, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding HCYT, under

> conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.
>
> Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

Thus, method for screening compounds that change the expression of SEQ ID NO: 14 (Claim 39) or a method for assessing toxicity of a test compound via nucleic acid expression profiling (Claim 41) is not disclosed in the specification. This is new matter.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 21, 23, 26, 27, 28, 30, 35, and 37 are rejected under 35 U.S.C. 102(a) as being anticipated by Heckel et al. (Nov. 1, 1997; Human Molecular Genetics 6(12): 2031-2041). Heckel et al. teach meningioma expressed antgen-6 (MEA-6) having 92.7% identity to SEQ ID NO: 6. See Figure 7 and the western blot in Figure 1D. Therefore, Heckel et al. teach an isolated polypeptide comprising an amino acid sequence that shares at least 90% identity to SEQ ID NO: 6, and biologically active and immunogenic fragments of SEQ ID NO: 6 (Claim 21). MEA-6 was placed in solution with PBS (page 2040, right col., under "Western blot analysis"; Claim 35).

At page 2032, left col., Heckel et al. teach that recombinant proteins (including MEA-6) were expressed from E. coli and screened with pre-absorbed patient serum (comprising antibodies) from patients having glioblastoma, neurinoma, and meningioma. Antigen (MEA-6):antibody complexes were detected by a secondary antibody binding to the constant region

of the human IgG-heavy chain. Thus, Heckel et al. teach a method for screening compounds that specifically bind to MEA-6 by combining MEA-6 with at least one test compound (serum antibodies) and detecting the MEA-6:antibody binding with a secondary antibody (Claim 37). The antibody which specifically binds to MEA-6 is taught by Heckel et al. (Claim 30). Indeed, given the high identity between MEA-6 and SEQ ID NO: 6, this antibody is considered to also specifically bind SEQ ID NO: 6.

Polynucleotide sequence encoding MEA-6 is taught in Figure 2 (Claim 23). This cDNA was inserted into ZAP Express ™ Expression System in sense orientation with respect to the lacZ promoter (bridging pages 2031-2032; Claim 26). E. coli host cells were transformed with this expression system (Claim 27), and the MEA-6 protein expressed therefrom and isolated (Claim 28).

Note that while Heckel et al. each MEA having 92.7% identity to SEQ ID NO: 6 and DNA encoding MEA-6, methods of detecting DNA encoding MEA-6 (page 2032, right col.) and methods of altering expression of this DNA via IPTG (Figure 1D), the DNA of Heckel et al. is wholly different from SEQ ID NO: 14, sharing 37% idenityt with SEQ ID NO: 14. Thus, Claims 31-34, 39, and 40 are not taught by Heckel et al.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cochrane Carlson, Ph.D. whose telephone number is 571-272-0946. The examiner can normally be reached on 7:00 AM - 4:00 PM, off alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen Cochrane Carlson PhD

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PRIMARY EXAMINER